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Signature: Takeshi Takemori

Takeshi Takemori

Date: September 3, 2009

JAPAN PATENT OFFICE

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[Name of matter] Specification 1

[Name of matter] Abstract 1

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[Name of Document] Specification

[Title of the Invention] AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

[Scope of Claims]

[Claim 1] An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

[Claim 2] The aqueous liquid preparation according to claim 1, wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenol residue, and the polyether alcohol is represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100.

[Claim 3] The aqueous liquid preparation according to claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

[Claim 4] The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

[Claim 5] The aqueous liquid preparation according to claim 1 or 4, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

[Claim 6] The aqueous liquid preparation according to any one of claims 1 to 3, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration

of 0.5 w/v %.

[Claim 7] The aqueous liquid preparation according to any one of claims 1, 2 and 4, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

[Claim 8] The aqueous liquid preparation according to any one of claims 1 to 7, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.

[Claim 9] The aqueous liquid preparation according to any one of claims 1 to 8, wherein benzalkonium chloride is contained as a preservative.

[Claim 10] The aqueous liquid preparation according to any one of claims 1 to 9, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

[Claim 11] The aqueous liquid preparation according to any one of claims 1 to 10, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

[Claim 12] The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

[Claim 13] The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

[Claim 14] The aqueous liquid preparation according to

any one of claims 1 to 12, wherein the aqueous liquid preparation is a nasal drop.

[Claim 15] An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

[Claim 16] An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

[Claim 17] A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

[Claim 18] A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

[Detailed Description of the Invention]

[0001]

[Technical Field to Which the Invention Pertains]

The present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. More particularly, the present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

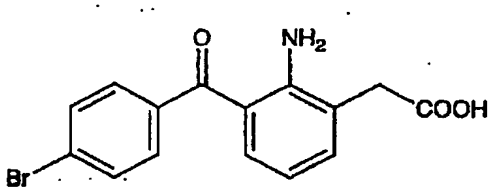
[0002]

[Conventional Art]

Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):

[0003]

[Chemical Formula 1]



[0004]

of which chemical name is 2-amino-3-(4-bromobenzoyl) phenylacetic acid are known (See Patent Literature 1). 2-Amino-3-(4-bromobenzoyl)phenylacetic acid, its pharmacologically acceptable salt and a hydrate thereof are known as a non-steroidal anti-inflammatory agent, and they are effective against inflammatory diseases of anterior or posterior segment of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in

the field of ophthalmology, and its sodium salt has been practically used in the form of eye drops (See Non-patent Literature 1).

[0005]

The eye drop as mentioned above is designed to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by means of addition of a water-soluble polymer (e.g. polyvinylpyrrolidone, polyvinyl alcohol, etc.) and a sulfite (e.g. sodium sulfite, potassium sulfite, etc.)(See Patent Literature 3).

In addition, as an eye drop other than the above-mentioned one, there is reported a stable ophthalmic composition which comprises incorporating an antibacterial quaternary ammonium polymer and boric acid into an acidic ophthalmic agent. The acidic agent includes, for example, 2-amino-3-(4-bromobenzoyl)phenylacetic acid (See Patent Literature 4).

[Patent Literature 1] JP-A-23052/1977

[Patent Literature 2] JP-A-126124/1987

[Patent Literature 3] Japanese patent No. 2,683,676

[Patent Literature 4] Japanese patent No. 2,954,356, column 6, lines 26-27, line 45

[Non-patent Literature 1] "New Drugs in Japan, 2001", 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, p.27-29

[0007]

[Problem to be Solved by the Invention]

It is an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically

acceptable salt thereof or a hydrate thereof, which is stable within a pH range giving no irritation to eyes and has a sufficient preservative effect.

[0008]

Another object of the invention is to provide a method for stabilizing an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

[0009]

Further, another object of the invention is to provide a method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and the preservative.

[0010]

[Means for Solving the Problem]

As a result of various studies, the inventors of the present invention have found that, by adding an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, the aqueous solution becomes stable within a pH range giving no irritation to eyes and has a sufficient preservative effect. The inventors of the present invention have further studied extensively and completed the present invention.

[0011]

Namely, the present invention relates to:

(1) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,

(2) The aqueous liquid preparation according to the above (1), wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenol residue, and the polyether alcohol is represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100,

(3) The aqueous liquid preparation according to the above (1) or (2), wherein the alkyl aryl polyether alcohol type polymer is tyloxapol,

(4) The aqueous liquid preparation according to the above (1), wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18,

(5) The aqueous liquid preparation according to the above (1) or (4), wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate,

(6) The aqueous liquid preparation according to any one of the above (1) to (3), wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %,

(7) The aqueous liquid preparation according to any one of the

above (1), (2) and (4), wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %,

(8) The aqueous liquid preparation according to any one of the above (1) to (7), wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %,

(9) The aqueous liquid preparation according to any one of the above (1) to (8), wherein benzalkonium chloride is contained as a preservative,

(10) The aqueous liquid preparation according to anyone of the above (1) to (9), wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

(11) The aqueous liquid preparation according to any one of the above (1) to (10), wherein the pH of the aqueous liquid preparation is within a range of 7 to 9,

(12) The aqueous liquid preparation according to the above (11), wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5,

(13) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is an eye drop,

(14) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is a nasal drop,

(15) An eye drop comprising sodium 2-amino-3-(4-

bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol,

(16) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate,

(17) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and

(18) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

[0012]

In the present invention, the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid includes, for example, an alkali metal salt such as sodium salt and potassium salt, and an alkaline earth metal salt such as calcium salt and magnesium salt, among which sodium salt is

especially preferable.

[0013]

2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in, for example, Patent Literature 1 or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic conditions and recrystallization conditions. The hydrate includes 3/2 hydrate.

[0014]

In the aqueous liquid preparation of the present invention, the content of 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 w/v %, and the content is appropriate varied depending on the purpose of use and the degree of disease to be treated.

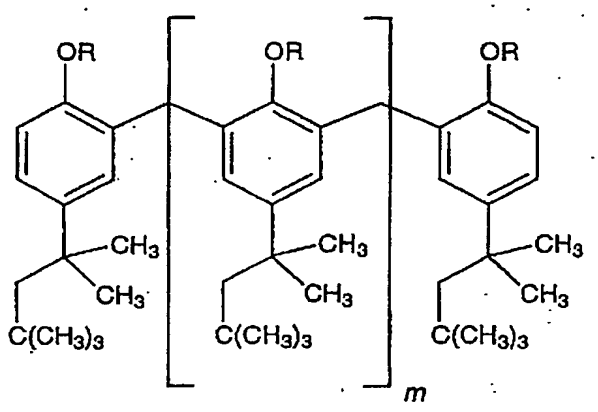
[0015]

The carbon number of alkyl in an alkyl aryl polyether alcohol type polymer (polymerization degree: 3 to 10) which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is approximately 1 to 18. Specifically, the alkyl group includes, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1,2-dimethylbutyl,

2-ethylbutyl, cyclopentyl, hexyl, cyclohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, isononyl, decyl, isodecyl, undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isooctadecyl, and isomers thereof, among which 1,1,3,3-tetramethylbutyl which is an isomer of octyl groups is especially preferable. The above-mentioned aryl can be preferably a phenol residue. The above-mentioned polyether alcohol can be represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100, preferably 5 to 30, more preferably 8 to 10. The average polymerization degree is preferably about 3 to 10. Among the above-mentioned alkyl aryl polyether alcohol type polymers, tyloxapol having the following structure is especially preferable.

[0016]

[Chemical Formula 2]



$R = (CH_2CH_2O)_xH$

$x = 8 - 10$

$m < 6$

[0017]

The fatty acid of the polyethylene glycol fatty acid ester which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be preferably a fatty acid having the carbon number of 12 to 18. Specific examples of such polyethylene glycol fatty acid esters are polyethylene glycol monostearate, polyethylene glycol monolaurate, polyethylene glycol monooleate, polyethylene glycol diisostearate, polyethylene glycol dilaurate, polyethylene glycol dioleate, and the like. Among these compounds, polyethylene glycol monostearate is preferable, and polyoxyl 40 stearate is especially preferable. The polyoxyl 40 stearate is a monostearic acid ester of an ethylene oxide condensed polymer, and can be represented by the formula $C_{17}H_{35}COO(CH_2CH_2O)_nH$ which is a non-ionic surfactant and n is about 40.

[0018]

Although the content of the alkyl aryl polyether alcohol type polymer in the aqueous liquid preparation of the present invention depends on the kind of compounds used, the minimum concentration is about 0.01 w/v % and the maximum concentration is about 0.5 w/v %. With respect to the tyloxapol content, for example, the minimum content is about 0.01 w/v %, 0.02 w/v % or 0.03 w/v %, and the mamximum content is about 0.05 w/v %, 0.1 w/v %, 0.3 w/v % or 0.5 % w/v, and preferably the minimum content is about 0.02 w/v % and the maximum content is about 0.05 w/v %.

[0019]

Although the content of the polyethylene glycol fatty acid ester in the aqueous liquid preparation of the present invention depends on the kind of compounds used, it is within a range of about 0.02 w/v % of minimum concentration to about 0.1 w/v % of maximum concentration. For example, the content of polyethylene glycol monostearate is within a range of about 0.02 w/v % of minimum content to about 0.1 w/v of maximum content, and preferably within a range of about 0.02 w/v % of the minimum content to about 0.05 w/v % of the maximum content.

[0020]

The incorporation ratio of tyloxapol in the aqueous liquid preparation of the invention is within a range of the minimum content of about 0.1 or 0.2 part by weight to the maximum content of about 0.5, 1, 3 or 5 parts by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

[0021]

The incorporation ratio of polyethylene glycol monostearate in the aqueous liquid preparation of the present invention is within a range of the minimum content of about 0.2 part by weight to the maximum content of about 0.5 or 1 part by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

[0022]

The preservative used in the present invention includes,

for example, quaternary ammonium salts (e.g. benzalkonium chloride, benzethonium chloride, etc.), chlorhexidine gluconate, and the like, among which benzalkonium chloride is especially preferable.

[0023]

Further, so long as the purpose of the present invention is achieved, conventional various additives such as isotonics, buffers, thickners, stabilizers, chelating agents, pH controlling agents, perfumes and the like may be appropriately added to the aqueous liquid preparation of the present invention. The isotonics include sodium chloride, potassium chloride, glycerine, mannitol, sorbitol, boric acid, glucose, propylene glycol and the like. The buffers include, for example, phosphate buffer, borate buffer, citrate buffer, tartarate buffer, acetate buffer, boric acid, borax, amino acids, and the like. The thickners include polyvinylpyrrolidone, carboxymethylcellulose, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, sodium polyacrylate, and the like. The stabilizers include sulfites such as sodium sulfite and the like. The chelating agents include sodium edetate, sodium citrate, condensed sodium phosphate and the like. The pH controlling agents include hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid and the like. The perfumes include 1-menthol, borneol, camphor, Eucalyptus oil, and the like.

[0024]

With respect to the concentrations of the above various

additives in the aqueous liquid preparation of the present invention, the isotonic is incorporated into an osmotic pressure ratio of about 0.8 to 1.2, and the concentrations of the buffer and the thickner to be added are about 0.01 to 2 w/v % and 0.1 to 10 w/v %, respectively.

[0025]

The pH of the aqueous liquid preparation of the present invention is adjusted to about 7 to 9, preferably about 7.5 to 8.5.

[0026]

So long as the purpose of the present invention is achieved, other same or different kind of active ingredients may be appropriately added.

[0027]

The aqueous liquid preparation of the present invention can be prepared by per se known method or according to the method as described in the Japanese Pharmacopoeia、14th Edition, General Rules for Preparations, Solutions or Ophthalmic solutions.

[0028]

The aqueous liquid preparation of the present invention can be applied to warm-blooded animals such as human, rat, mouse, rabbit, cow, pig, dog, cat, and the like.

[0029]

The aqueous liquid preparation of the present invention, for example, in the form of an eye drop, can be used for the treatment of inflammatory diseases in anterior or posterior segment of the eye such as blepharitis, conjunctivitis,

scleritis, postoperative inflammation, and the like. The dose of the aqueous liquid preparation containing 0.1 w/v % of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate is, for example, administered to an adult 3 to 6 times daily in an amount of 1 to 2 drops per one time. Depending on the degree of diseases, frequency of dosing is appropriately controlled.

[0030]

[Examples]

The present invention is illustrated by way of the following Experimental Examples and Working Examples, but the present invention is not restricted to these Examples.

[0031]

Experimental Example 1: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

(Experimental Method)

Four eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to stability test at 60°C.

[0032]

[Table 1]

Component	Comparison Example 1	A-01	A-02	A-03
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	-	-	-
Polyoxyl 40 stearate	-	0.15 g	-	-
Tyloxapol	-	-	0.15 g	0.02 g
Sterile purified water	q.s.	q.s.	q.s.	q.s
Total volume	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
60°C-4W	51.3	63.7	73.8	89.6

[0033]

The remaining rate (%) in the above Table 1 indicates values obtained by correcting the content of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate taking into account moisture vaporization from the container. As is apparent from the Table 1, stability test was carried out under the conditions of pH 7.0 at 60°C for 4 weeks, and sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in each eye drop was stable in the order of tyloxapol-containing preparation > polyoxyl 40 stearate-containing preparation > polysorbate 80-containing preparation.

Further, with respect to eye drops containing tyloxapol, sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the composition containing 0.02 w/v % of tyloxapol is more stable

than that in the composition containing 0.15 w/v % of tyloxapol.

[0034]

Experimental Example 2: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

(Experimental Method)

Five eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, filled respectively into a polypropylene container and preserved at 60°C for 4 weeks, and then the content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid and the pH in each eye drop were measured.

Table 2 shows the remaining rate and the pH of sodium 2-amino-3-(4- bromobenzoyl)phenylacetate after storage at 60°C for 4 weeks, when the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate at the time of production of eye drops is set to 100%. The remaining rate is a corrected value taking into account moisture vaporization from the container.

[0035]

[Table 2]

Components		A−04	A−05	A−06	A−07	A−08
Sodium 2-amino-3-(4-bromobenzoyl)phenyl-acetate		0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Borax		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Benzalkonium chloride		0.005g	0.005g	0.005g	0.005g	0.005g
Polysorbate 80		—	—	—	—	—
Tyloxapol		0.02 g	0.05 g	0.03 g	—	—
Polyoxyl 40 stearate		—	—	—	0.02 g	0.05 g
Polyvinyl-pyrrolidone (K-30)		2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
Sodium edetate		0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Sodium hydroxide		q.s.	q.s.	q.s.	q.s.	q.s.
Sterile purified water		q.s.	q.s.	q.s.	q.s.	q.s.
Total volume		100 mL	100 mL	100 mL	100 mL	100 mL
pH		8.17	8.16	8.15	8.19	8.19
60°C-4W	Remaining rate	92.6	90.9	92.0	93.4	93.1
	pH	8.15	8.16	8.15	8.13	8.14

[0036]

As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions containing 0.02 w/v %, 0.03 w/v % and 0.05 w/v % of tyloxapol or 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60°C for 4 weeks, which indicates

that those compositions have sufficient stability for eye drops.

[0037]

Experimental Example 3: Preservative effect test of aqueous liquid preparation containing sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Preservative effect test of compositions A-04, A-05 and A-07 of Experimental Example 2 was carried out.

The results are shown in Table 3.

[0038]

[Table 3]

Table 3-1

A−04	Inoculum count	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^{6}	3.0×10^{1}	0	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Unit: CFU/mL

Table 3-2

A−05	Inoculum count	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^{6}	1.7×10^{5}	2.0×10^{1}	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Unit: CFU/mL

Table 3-3

A−07	Inoculum count	6th	24th	1W	2W	3W	4W
S. aureus	2.7×10^{6}	3.1×10^{4}	0	0	0	0	0
E. coli	7.4×10^{6}	0	0	0	0	0	0
P. aeruginosa	8.8×10^{6}	0	0	0	0	0	0
C. albicans	4.6×10^{5}	—	—	0	0	0	0
A. niger	1.0×10^{5}	—	—	0	0	0	0

Unit: CFU/mL

[0039]

As is apparent from Tables 3-1, 3-2 and 3-3, the preservative effect of composition A-04 was found to be compatible with EP-criteria A [1)], and those of compositions A-05 and A-07 were found to be compatible with EP-criteria B [2)].

[0040]

1) EP(European Pharmacopoeia)-criteria A

Viable cell counts of bacteria (*S. aureus, P.aeruginosa*) 6 hours, 24 hours, and 28 days after inoculation decrease to not more than 1/100, not more than 1/1000, and undetectable, respectively.

Viable cell count of fungi (*C. albicans, A. niger*) 7 hours after inoculation decreases to not more than 1/100, and thereafter, the cell count levels off or decreases.

2) EP-criteria B

Viable cell counts of bacteria (*S. aureus, P.aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases.

Viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

[0041]

Example 1: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl) phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edentate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.17

An eye drop is prepared using the above components in a conventional manner.

[0042]

Example 2: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl) phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.05 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.16

An eye drop is prepared using the above components in a conventional manner.

[0043]

Example 3: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl) phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Polyoxyl 40 stearate	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.19

An eye drop is prepared using the above components in a conventional manner.

[0044]

[Effect of the Invention]

According to the present invention, a stable aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be prepared by incorporating an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. Also, an aqueous liquid preparation of the present invention, wherein a preservative is incorporated, has a

sufficient preservative effect.

Therefore, the aqueous liquid preparation of the present invention is advantageously used as an eye drop for the treatment of, for example, blepharitis, conjunctivitis, scleritis, and postoperative inflammation. In addition, such aqueous liquid preparation can be used as a nasal drop for the treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

[Name of Document] Abstract

[Abstract]

[Problem]

To provide an aqueous liquid preparation containing stabilized 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof, which is stable and exhibits a sufficient preservative effect.

[Means for solving the problem]

An aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof and an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate.

[Chosen Drawing] None

Applicant's History Information

Identification Number: [000199175]

1. Date of Change August 22, 1990
[Reason for Change] Newly recorded
Address: 5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, OSAKA
Name: SENJU PHARMACEUTICAL CO., LTD.